Remarks/Arguments

I. Claim Rejections under 35 USC §103(a)

Claims 23-41, 48, 50-54, 63, 81-82, 85, 141, 143, 166-189, 192-205, 208-218, 221-233, 236-248, and 250-269 are rejected under 35 USC §103(a) as being unpatentable over Farazi et al. in view of Roelant.

In making the rejections, the Office Action states that Farazi et al. teach that 1) mutants of human IMPDH type II are resistant to inhibitors of wild-type IMPDH; 2) inhibitors of IMPDH have antiproliferative activity; 3) MPA (mycophenolic acid), MPA derivatives and mycophenolate mofetil are specific inhibitors of IMPDH; 4) mutant IMPDH confers resistance to and is very useful in anti-infective chemotherapy by designing species-selective IMPDH inhibitors. The Office Action further asserts that " in the state of the art, there are many methods through which one can ascertain the result of a mutagenized enzyme. One way is to perform cell proliferation assays since inhibitors of IMPDH have antiproliferative activity where resistance against the inhibitors of IMPDH corresponds to an increase in the proliferation of the cells containing the mutant IMPDH."

The Office Action continues to assert that the difference between the instant invention and the reference of Farazi et al. is that the reference of Farazi et al. does not teach cell proliferation assays. The Office Action then asserts that cell proliferation assays are well known by citing Roelant and the Stratagene Catalog. The Office Action concludes that "it would be obvious to one having ordinary skill in the art at the time the claimed invention was made to use the mutant of Farazi et al. and screen whether the

mutants have resistance against inhibitors of IMPDH by performing cell proliferation assays, quantifying viable cells containing the mutant enzymes and cells containing wild-type IMPDH."

To the extent the rejection can be applied to the amended claims, Applicant respectfully traverses.

At the onset, Applicant notes that there may exist methods through which one having ordinary skill in the art may ascertain or screen the result of a mutagenized enzyme as asserted in the Office Action. However, it is one thing to use a method to ascertain or screen the result of a mutagenized enzyme, wherein, prior to the conducting of the method, it is not known whether the mutagenized enzyme is or is not resistant to inhibitors. It is quite another thing to employ methods as claimed herein to sustain the proliferation and/or viability of cells to which a nucleic acid encoding a mutagenized enzyme is introduced and the mutant enzyme is resistant to inhibitors or conditions that inhibit the wild-type enzyme.

With respect to a method for ascertaining the result of a mutagenized enzyme, Farazi et al. disclose the use of *E.coli* strain H712 to ascertain the result of mutagenized enzyme (Page 962, the last paragraph of the left column continued to the first paragraph of the right column). According to Farazi et al., a library of randomly mutagenized pHIA5 was created by transforming pHIA5 (containing the human IMPDH type II coding sequence) into *E.coli* strain NR9072. Id. The mutagenized plasmid was then transformed into *E.coli* strain H712 to select MPA resistant colonies growing on minimal media containing MPA. Id. The plasmid isolated from the selected MPA

resistant colonies was again transformed into H712 cells and the transformants were tested for the ability to grow on minimal medium in the presence of MPA. Id.

It appears that Farazi et al. disclose a method of ascertaining or screening a mutagenized enzyme using *E.coli*, wherein the nature of the mutagenized enzyme is not known prior to the screening. However, Farazi et al. do not teach or suggest that cells can be selectively proliferated using an altered enzyme known to be resistant to inhibitors or conditions that inhibit an unaltered enzyme. More importantly, Farazi et al. do not suggest or teach at all the introduction of a nucleic acid encoding a mutagenized enzyme into eukaryotic cells.

With respect to cell proliferation assays, Roelant teaches a process of quantifying the number of viable cells in an aqueous suspension using an energy-emitting non-hazardous probe and a probe trigger. Like the Statagene Catalog, Roelant teaches a method of quantifying the number of cells. While the cells in the Stratagene Catalog are cultured cells in tissue culture, the cells in Roelant are "viable cells" which are "cells whose structure and function are intact" and include "fresh cells isolated from a living organism, cells grown or cultured *in vitro*, or cells reconstituted from frozen or freeze-dried preparations" (ll. 59-63, col. 5, the Roelant patent). In addition, the cells in Roelant are in an aqueous suspension (See Abstract and Claims).

Yet, neither Roelant nor Stratagene teaches how to proliferate cells, much less selective proliferation and/or viability of a first cell into which a nucleic acid encoding an altered enzyme is introduced, wherein the altered enzyme is resistant to inhibitors or conditions, as opposed to a second cell that does not contain the altered enzyme. In

addition, neither Roelant nor Stratagene teaches a method of quantifying the proliferation of *E.Coli.*

It has been long established that to establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation to modify or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Based on these well-established principles, Applicant notes that there is no suggestion or motivation to combine the references together. The Office Action asserts that the motivation of performing the cell proliferation assays is to determine if the mutant IMPDH is resistant to IMPDH inhibitors. However, the factual inquiry into motivation to combine reference "could not be resolved on subjective belief and unknown authority" but "must be based on objective evidence of record." *In re Sang Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002).

In fact, it would be against common knowledge or wisdom in the art to perform the cell proliferation assays of Roelant or Stratagene to ascertain the mutant enzymes of Farazi et al. In particular, Farazi et al. used one *E.coli* strain to screen mutagenized enzymes. The growth or formation of *E.coli* colonies on minimal media in the presence of MPA directly indicates that the *E.coli* colonies may contain mutagenized enzymes that are resistant to MPA (the first paragraph of the right column, page 962). On the other hand, Roelant teaches a method of quantifying viable cells <u>in an aqueous suspension</u> of cells (See Abstract and Claims), not *E.coli* colonies on minimal media. Stratagene teaches a method of quantifying the number of cells <u>in tissue culture</u>, not

E.coli colonies on minimal media. Applicant is at loss as to how one of ordinary skill in the art would be motivated to use the cell proliferation assay of Roelant, which requires cells in an aqueous suspension, or that of Stratagene, which requires cells in tissue culture, to ascertain or screen the mutant enzyme of Farazi et al., which is selected by *E.coli* colonies growing on minimal media.

Even if, against well-accepted wisdom, the references were to be combined as proposed in the Office Action, the hypothetical combination would not arrive at all the limitations of the amended claims. In particular, the hypothetical combination would be a method of screening mutagenized enzymes by performing cell proliferation assays in *E.coli*, wherein the mutagenized enzymes' relationship to inhibitors are unknown. The Office Action appears to agree with this. Based on the untenable assumption that there is a motivation to perform the cell proliferative assay of Roelant (or the Stratagene Catalog) to ascertain mutant enzymes of Farazi et al., the Office Action asserts that "it would be obvious to one having ordinary skill in the art at the time the claimed invention was made to use the mutant of Farazi et al. and screen whether the mutants have resistance against inhibitors of IMPDH by performing cell proliferation assays. . . ." (See page 3, the last paragraph of the Office Action.)

However, the amended claims are directed to methods of providing for selective proliferation, viability, or proliferation and viability of the eukaryotic cells to which a nuclei acid encoding an altered enzyme is introduced, wherein the altered enzyme is resistant to an inhibitor or a condition that inhibits the unaltered enzyme, as opposed to the eukaryotic cells that do not contain the altered enzyme. The hypothetical combination does not teach, *inter alia*, eukaryotic cells. It follows that the hypothetical combination does not teach or suggest all the limitations of the amended claims.

Finally, since Farazi et al. merely teach the introduction of mutagenized enzymes into *E.coli* to screen for inhibitor-resistant enzymes, one of ordinary skill in the art would not have had a reasonable expectation of success with respect to the methods in the amended claims.

In light of the foregoing, Applicant finds no support for teaching or motivation to combine the references. The hypothetical combination does not teach all the limitations of the amended claims. And, there is no reasonable expectation of success. Accordingly, Applicant respectfully requests that the rejections of claims 23-41, 48, 50-54, 63, 81-82, 85, 141, 143, 166-189, 192-205, 208-218, 221-233, 236-248, and 250-269 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

II. Allowable Subject Matter

Claims 73-74, 142-143, 190-191, 206-207, 219-220, 234-235, 248-249 and 260-261 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Newly added claims 270-285 corresponds to claims 73-74, 142-143, 190-191, 206-207, 219-220, 234-235, 248-249 and 260-261 which are rewritten in independent form including all of the limitations of the base claim and any intervening claims. Accordingly, Applicant respectfully requests that the objections be withdrawn and claims 270-285 be allowed.

Applicant believes that the present amendment places the application in condition for allowance. A Notice of Allowance is, therefore, respectfully requested. If any additional issue needs to be addressed to expedite the prosecution of this application, please feel free to call the undersigned at (310) 788-3218.

Respectfully submitted,
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